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High-Dose Intravenous Vitamin C and Mortality and Organ Dysfunction in Severe Burn Injury

The VICTORY Randomized Clinical Trial

Christian Stoppe, MD; Aileen Hill, MD; Leopoldo C. Cancio, MD; Andrew G. Day, MSc; Kaitlin A. Pruskowski, PharmD; Alexis F. Turgeon, MD; Tam Pham, MD; Sylvain Bélisle, MD; Mario Aurelio Martínez-Jiménez, MD; Ulrich Limper, MD; Jochen Gille, MD; Jon Wisler, MD; Alisa Savetamal, MD; Jonathan Pollack, MD; Daisy Grau Domínguez, MD; Serge Jennes, MD; Jeffrey W. Shupp, MD; Marc G. Jeschke, MD; Kirsten Colpaert, MD, PhD; Gabriel Hundeshagen, MD; Justus P. Beier, MD; Pornprom Muangman, MD; Ann Echeverri McCandless, MD; Patrick Meybohm, MD; Tilman Grune, MD; Ellen Dresen, PhD; Daniela Weber, PhD; Carina Güttler, MSc; Charles Chin Han Lew, PhD; Xuran Jiang, BM, MSc; Shawna Froese, BSc; Maureen Dansereau, BSc; Zheng-Yii Lee, PhD; Daren K. Heyland, MD; for the VICTORY Study Team

IMPORTANCE Severe burn injury triggers systemic inflammation that can lead to multiple organ dysfunctions and death. High-dose intravenous vitamin C has been proposed to mitigate these effects, but strong evidence in patients with burn injury is lacking.

OBJECTIVE To evaluate the efficacy of high-dose intravenous vitamin C in patients with severe burn injury.

DESIGN, SETTING, AND PARTICIPANTS Randomized, double-blind, placebo-controlled phase 3 trial conducted across 24 burn centers in North, Central, and South America; Europe; and Asia. Adults (≥18 years) with deep second- and/or third-degree burns covering 20% or more of total body surface area and requiring skin grafting were enrolled between August 18, 2020, and September 12, 2025. Final follow-up was completed in March 2026. The trial was stopped early after the first prespecified interim analysis for futility/harm.

INTERVENTIONS Patients were randomly assigned (1:1) to receive intravenous vitamin C (50 mg/kg every 6 hours for 96 hours) or matched placebo.

MAIN OUTCOMES AND MEASURES The primary outcome was a composite of 28-day mortality and persistent organ dysfunction (defined as dependence on mechanical ventilation, kidney replacement therapy, or vasopressor/inotrope support at day 28). The main secondary outcome was time to discharge alive from hospital within 90 days.

RESULTS Among 238 patients enrolled (mean age, 48.9 [SD, 19.1] years; 79% male; mean total body surface area, 37.0% [SD, 14.6%]), 120 were assigned to vitamin C and 118 to placebo. The primary composite outcome occurred in 49 patients (40.8%) in the vitamin C group and 35 patients (29.7%) in the placebo group (adjusted risk ratio [RR], 1.28 [95% CI, 0.99-1.65]; $P = .06$), crossing the prespecified futility/harm threshold and prompting early trial termination. Time to discharge alive from hospital within 90 days was not improved (adjusted subdistribution hazard ratio, 0.85 [95% CI, 0.62-1.16]; $P = .31$). Twenty-eight–day mortality was higher in the vitamin C group (15.0% vs 7.6%; adjusted RR, 1.96 [95% CI, 1.32-2.90]; $P = .001$), as was hospital mortality (23.3% vs 16.1%; adjusted RR, 1.44 [95% CI, 1.03-2.00]; $P = .03$).

CONCLUSIONS AND RELEVANCE Among patients with severe burn injury, high-dose intravenous vitamin C did not reduce 28-day mortality and persistent organ dysfunction and is possibly harmful.

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Editorial
Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The VICTORY Study Team investigators appear in Supplement 2.

Corresponding Author: Christian Stoppe, MD, Department of Anaesthesiology and Intensive Care, Emergency and Pain Medicine, University Hospital Würzburg, Oberdürrbacher-Straße 6, 97080 Würzburg, Germany (christian.stoppe@gmail.com).

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Severe burn injury is a leading cause of unintentional injury and disability-adjusted life-years worldwide, particularly among young and middle-aged adults. Despite advances in critical care, mortality rates have plateaued since the 1980s, and many survivors endure long-term physical disability, psychological sequelae, and substantial social and economic burdens that extend to their families.[1]

Central to these outcomes is a pathophysiological cascade triggered by massive release of oxygen-free radicals, which causes vascular endothelial injury and capillary leakage, culminating in shock, profound systemic inflammation, and tissue edema.[2,3]

Vitamin C is a compelling therapeutic candidate to disrupt this cascade because it directly scavenges the excess free radicals implicated in postburn macromolecular damage.[4,5] Beyond its antioxidant capacity, vitamin C can potentially restore vascular responsiveness, ameliorates microcirculatory flow, preserves endothelial barrier function, augments bacterial defense, and may support wound healing.[6-9] In patients with burn injuries, these mechanisms might translate into reduced endothelial injury and capillary leakage, decreasing the overwhelming fluid requirements and potentially mitigating fluid-associated complications and protecting organ function.[10]

High-dose intravenous vitamin C has been associated with significant reductions in resuscitation fluid volume and ventilator duration in severely burned patients.[4,11-14] While meta-analyses of trials in sepsis and general critical illness showed a potential mortality benefit,[15] the LOVIT (Lessening Organ Dysfunction With Vitamin C) trial, a rigorous, multicenter study in patients with septic shock, found an increased risk of death or persistent organ dysfunction with the use of high-dose intravenous vitamin C.[16] This equipoise underscores that the efficacy and safety of intravenous vitamin C are likely context-specific, and data from medical or septic shock populations may not be extrapolated to the distinct pathophysiology, fluid dynamics, and mortality risk profile of severe burn injury.[17] This lack of high-level evidence stands in contrast to some international nutrition guidelines suggesting micronutrient supplementation including vitamin C for patients with burns.[13]

The Vitamin C in Thermal Injury (VICTORY) trial was conceived to test the hypothesis that administration of high-dose intravenous vitamin C would improve the composite end point of 28-day mortality and persistent organ dysfunction in patients with severe burn injury.

Key Points

Question Does high-dose intravenous vitamin C reduce a composite of 28-day mortality and persistent organ dysfunction in patients with severe burn injury?

Findings In this randomized clinical trial that included 238 patients with severe burns, the primary composite outcome of 28-day mortality and persistent organ dysfunction occurred in 40.8% of patients in the intravenous vitamin C group compared with 29.7% in the placebo group. At the first prespecified interim analysis, this result crossed the futility/harm threshold, prompting early termination of the trial.

Meaning High-dose intravenous vitamin C did not reduce mortality and organ dysfunction and may be associated with harm in patients with severe burn injury.

Methods

The VICTORY trial was an international, parallel-design, randomized double-blind, placebo-controlled, phase 3 trial conducted across 24 burn centers in North, Central, and South America; Europe; and Asia. The protocol (available in Supplement 1) was approved by national regulatory agencies and the research ethics board or institutional review board at each participating site (a complete list of sites and agencies is provided in Supplement 2 and Supplement 3, respectively). Written informed consent was obtained from patients or their legally authorized representatives. Where permitted, deferred consent or consent from an independent physician was used, and follow-up consent obtained from the patient or next of kin when available. An independent data and safety monitoring board (DSMB) provided oversight of the trial (Supplement 3). The trial was centrally coordinated by the Clinical Evaluation Research Unit at Queen's University, Kingston, Canada, with support from the study team at the University Hospital Würzburg, Würzburg, Germany (Supplement 3). This report follows the CONSORT (Consolidated Standards of Reporting Trials) guideline for randomized clinical trials.

Participants

Eligible patients were adults (≥18 years) with deep second- and/or third-degree burns covering 20% or more of total body surface area who were deemed to require skin grafting. In all potentially eligible patients, the attending burn surgeon was responsible for assessing burn depth using local standard criteria (eg, appearance, sensation, capillary refill) and confirming the need for skin grafting. Key exclusion criteria were presentation more than 24 hours after injury, known glucose-6-phosphate dehydrogenase deficiency, a history of kidney stones within the previous year, and concurrent use of hydroxocobalamin for suspected cyanide poisoning. A complete list of eligibility criteria and changes over time is available in the eMethods in Supplement 3.

Randomization and Blinding

Patients were randomly assigned in a 1:1 ratio to receive either intravenous vitamin C (ascorbic acid) or matching placebo. Randomization was performed through a centralized, secure web-based system using permuted blocks of 2, 4, and 6, stratified by clinical centers. All patients, clinical and trial staff, investigators, and outcome assessors remained blinded to treatment assignments throughout the trial. Only the site research pharmacist preparing the study product was unblinded to the group allocation.

Interventions

Patients in the intervention group received intravenous vitamin C at a dose of 50 mg/kg of preburn body weight (maximum, 150 kg) every 6 hours for 96 hours. The infusion rate did

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not exceed 100 mg/min to minimize the risk of infusion-related adverse events. The placebo group received an identical volume of either 5% dextrose in water or 0.9% sodium chloride administered on the same schedule.

Sites used vitamin C products available locally or provided by the coordinating center, according to product availability and regulatory approvals. A complete list of products is provided in the eMethods in Supplement 3. Study pharmacies diluted each 50-mg/kg dose in either 5% dextrose in water or 0.9% sodium chloride to achieve a final concentration of 1 to 25 mg of ascorbic acid per mL, with the admixture made isotonic prior to infusion as needed. Regardless of the specific product used, all sites adhered strictly to the same dilution and infusion protocol, ensuring consistency of the intervention across the trial (eMethods in Supplement 3). Open-label intravenous vitamin C for nutrient repletion was permitted at a maximum dose of 200 mg per day. Fluid resuscitation during the first 24 hours followed local protocols. Most sites used crystalloid-based regimens guided by the modified Brooke formula (2-4 mL of crystalloid per kg per percent total body surface area burned) or similar institutional adaptations, using Ringer lactate or Plasma-Lyte. Colloids (eg, 5% albumin) and blood products were administered at the discretion of the treating team, typically for refractory hypotension or after 24 hours. No fluid protocol was mandated by the trial. However, all sites were encouraged to adhere to standard burn resuscitation guidelines.

Outcomes

The primary outcome was a composite of 28-day mortality and persistent organ dysfunction, defined as dependence on mechanical ventilation, kidney replacement therapy (KRT), or vasopressor/inotrope support at 28 days after randomization.

Secondary outcomes include time to discharge alive from the hospital within 90 days (prespecified as most important), the individual components of 28-day persistent organ dysfunction including mortality, and 28-day persistent organ dysfunction-free days. For persistent organ dysfunction-free days, we summed the number of days in the first 28 days after intensive care unit (ICU) admission entirely free of mechanical ventilation, KRT, and vasopressor/inotrope support but assigned people who died within 28 days a value of -1 free days. We considered someone free of mechanical ventilation only if they remained free of ventilation for at least 48 consecutive hours; we considered a patient to be receiving KRT for every day from initiation to final discontinuation, regardless of whether KRT was delivered on intervening days.

Prespecified tertiary outcomes include hospital and 6-month mortality, ICU readmission rate, duration of mechanical ventilation, ICU and hospital length of stay, gram-negative bacteremia, 6-month health-related quality of life (36-Item Short Form Health Survey), and activities of daily living. Prespecified events of interest for safety assessment and post hoc outcomes are listed in the eMethods in Supplement 3.

Subgroup Analysis

The following prespecified subgroup analyses were performed: age, total body surface area of burns, SOFA (Sequential Organ Failure Assessment) score, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and timing of vitamin C administration. Subgroup analysis of presence of trauma and traumatic brain injury was not performed due to the very small subgroup sample size. Subgroup analysis of direct arrival vs transfer from other settings was not performed because data could not be uniformly collected. Early vs delayed initiation of intravenous vitamin C was added as post hoc subgroup analysis. The cutoff values for defining the subgroups were based on median value.

Statistical Analysis

We planned a total sample size of 333 patients per group, which would provide 78% power at 2-sided $\alpha = .05$ if the rate of 28-day persistent organ dysfunction or death decreased from 27% to 18% while allowing for 2 interim analyses for futility/safety. The operating characteristics of the trial under the prespecified futility rule (adjusted risk ratio [RR] >1.1 favoring control) were determined through trial simulations. Under the assumed treatment effect (RR of 0.67 for the primary outcome), the futility rule would reduce the power from 79% to 78% and introduced only minimal bias (mean RR of 0.68 vs true RR of 0.67). Detailed simulation results are provided in the trial protocol in Supplement 1 and eTable 1 in Supplement 3. As confirmed by the simulations, the stopping rule does not inflate type I error because there is no interim test for efficacy.

The analyses followed the intention-to-treat principle, with no postrandomization exclusions for the main analyses. All adjusted analyses control for age, total body surface area burned, baseline mechanical ventilation, and site.

For the primary outcome, we used modified Poisson regression with robust standard errors clustering by site. Results are presented as adjusted RRs with 95% CIs.

For the key secondary outcome of time to discharge alive, we treated death as a competing event precluding discharge alive. The cumulative incidence function was presented for each group, and between-group differences were assessed using the Fine and Gray subdistribution hazard model, with site included as a random effect (shared frailty) to account for clustering and fixed effects for the treatment indicator and other covariates. Time to ICU discharge alive was analyzed similarly. Hospital and ICU outcomes were censored at 91 days after randomization. We report the win ratio of persistent organ dysfunction-free days with 95% CIs estimated by the percentile bootstrap (n = 10 000) and tested for difference by the Wilcoxon rank-sum test.

Unadjusted absolute effect estimates with 95% CIs are given for all outcomes reported in the article. For binary outcomes, we report risk differences with exact 95% CIs. For 6-month mortality and 90-day cumulative incidence of discharge alive, we report between-group differences with 95% CIs estimated by the Wald method. For outcomes reported as medians, we report the difference in medians with 95% CIs estimated by the percentile method of 10 000 within-group bootstrap samples.

For the primary and main secondary outcome, we performed subgroup analysis by adding a subgroup indicator

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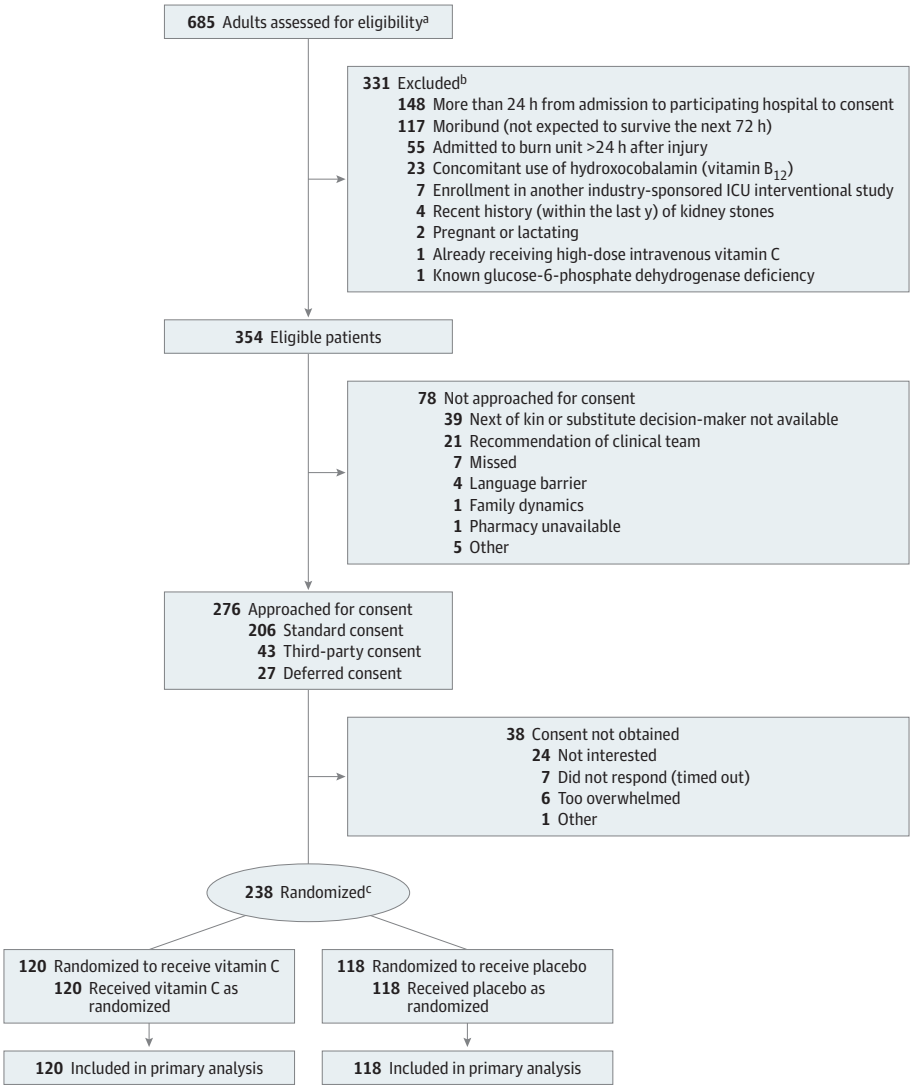
Figure 1. Flow Diagram of the VICTORY Randomized Clinical Trial


685 Adults assessed for eligibility[a]
331 Excluded[b]
148 More than 24 h from admission to participating hospital to consent
117 Moribund (not expected to survive the next 72 h)
55 Admitted to burn unit >24 h after injury
23 Concomitant use of hydroxocobalamin (vitamin B_{12})
7 Enrollment in another industry-sponsored ICU interventional study
4 Recent history (within the last y) of kidney stones
2 Pregnant or lactating
1 Already receiving high-dose intravenous vitamin C
1 Known glucose-6-phosphate dehydrogenase deficiency
354 Eligible patients
78 Not approached for consent
39 Next of kin or substitute decision-maker not available
21 Recommendation of clinical team
7 Missed
4 Language barrier
1 Family dynamics
1 Pharmacy unavailable
5 Other
276 Approached for consent
206 Standard consent
43 Third-party consent
27 Deferred consent
38 Consent not obtained
24 Not interested
7 Did not respond (timed out)
6 Too overwhelmed
1 Other
238 Randomized[c]
120 Randomized to receive vitamin C
120 Received vitamin C as randomized
118 Randomized to receive placebo
118 Received placebo as randomized
120 Included in primary analysis
118 Included in primary analysis

ICU indicates intensive care unit.

[a]Assessed patients were 18 years or older, had deep second- and/or third-degree burns covering 20% or more of total body surface area, and were deemed to require skin grafting.

[b]Patients could be excluded for multiple reasons.

[c]Randomization was stratified by clinical center using permuted blocks of size 2, 4, and 6.

and a subgroup × treatment interaction term to the adjusted models.

Two interim analyses for futility and harm were preplanned after 33% (n = 222) and 66% (n = 444) of patients had 28-day outcome data. The predefined stopping rule for futility/harm was based on the primary composite outcome of 28-day mortality and persistent organ dysfunction, with an adjusted RR greater than 1.1 favoring the control group triggering consideration of early termination.

This threshold was crossed at the first interim analysis, prompting the DSMB to recommend termination of the trial.

All analyses were performed using SAS version 9.4 (SAS Institute Inc); subgroup dot and whisker plots were created in R version 4.1.0 (R Foundation for Statistical Computing). All *P* values are 2-sided without adjustment for multiplicity. However, we report *P* values only for the primary, secondary, and safety outcomes, including mortality. All tertiary outcomes and subgroup analyses are considered exploratory, so 95% CIs are not adjusted for multiplicity. Further details and statistical analysis plan are available in VICTORY Protocol V3.2.1 in Supplement 1 and the eMethods in Supplement 3.

Results

Patient Enrollment and Characteristics

Between August 18, 2020, and September 12, 2025, among 685 patients assessed for eligibility, a total of 276 of 354 eligible patients were approached for consent, and 238 patients who provided consent were randomized to receive high-dose intravenous vitamin C (n = 120) or placebo (n = 118) (**Figure 1**). Baseline demographic and clinical characteristics were well-balanced between the 2 groups (**Table 1**; eTable 2 in Supplement 3). The mean age was 48.9 (SD, 19.1) years, and 188 patients (79.0%) were male. The mean total body surface area burned was 37.0% (SD, 14.6%); among patients

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with complete data, the mean APACHE II score was 15.8 (SD, 7.4). A total of 136 patients (57.1%) were receiving mechanical ventilation at randomization, and 135 patients (56.7%) required ventilation for 72 hours or longer.

Adherence to Protocol and Cointerventions

Adherence to the study intervention was high and similar between groups (eTable 3 in Supplement 3). Overall, 187 patients (78.6%) received all 16 doses of study product within the 96-hour treatment window (vitamin C, 78.3%; placebo, 78.8%). Among the 51 patients (21.4%) who did not complete all doses, 40 (16.8%) died, were discharged, or withdrew consent within the 96-hour treatment period. The mean time from ICU admission to first study dose was 14.6 (SD, 8.3) hours, and adherence to administered intravenous doses was 99.6% overall.

Protocol violations related to study intervention were documented in 30 patients (eTable 4 in Supplement 3). Open-label vitamin C exceeding permitted doses occurred exclusively in the placebo group (3 patients), and dispensing or dosing errors occurred in 3 patients (1 in the vitamin C group, 2 in the placebo group).

Primary Outcome

The primary composite outcome of 28-day mortality and persistent organ dysfunction occurred in 49 patients (40.8%) in the vitamin C group and 35 patients (29.7%) in the placebo group (adjusted RR, 1.28 [95% CI, 0.99-1.65]; $P = .06$) (**Table 2**). eTable 5 in Supplement 3 provides the components of persistent organ dysfunction over 28 days. At 28 days, mortality was 15.0% (n = 18) in the vitamin C group vs 7.6% (n = 9) in the placebo group (adjusted RR, 1.96 [95% CI, 1.32-2.90]; $P = .001$) (Table 2).

Subgroup analyses for the composite outcome demonstrated consistent lack of treatment benefit across all subgroups, with no evidence of heterogeneity ($P > .05$ for interaction for all) (eFigure 1 in Supplement 3).

Secondary Outcomes

The cumulative incidence of live discharge by 90 days is shown in **Figure 2** and was 65.5% (95% CI, 56.2%-73.4%) in the vitamin C group and 71.2% (95% CI, 62.0%-78.5%) in the placebo group (adjusted hazard ratio, 0.85 [95% CI, 0.62-1.16]; $P = .31$) (**Table 3**). Subgroup analyses for time to discharge alive showed a consistent lack of treatment benefit across all subgroups (for all, $P > .05$ for interaction) (eFigure 2 in Supplement 3). The cumulative distribution of 28-day persistent organ dysfunction-free days is shown in eFigure 3 in Supplement 3. The median persistent organ dysfunction-free days was 12.5 (IQR, 0-27.5) days for the vitamin C group vs 19.5 (IQR, 0.0-28.0) days for the placebo group (difference in median, -7.0 [95% CI, −17.0 to 4.0]). The win ratio for persistent organ dysfunction-free days was 0.75 (95% CI, 0.53-1.05; $P = .09$) favoring the control group.

Tertiary Outcomes

ICU mortality occurred in 27 patients (22.5%) in the vitamin C group vs 18 patients (15.3%) in the placebo group (adjusted RR, 1.43 [95% CI, 1.00-2.04]; $P = .05$). Hospital mortality was 23.3% (n = 28) in the vitamin C group and 16.1% (n = 19) in the placebo group (adjusted RR, 1.44 [95% CI, 1.03-2.00]; $P = .03$).

Table 1. Participant Characteristics[a]

Characteristic	Vitamin C (n = 120)	Placebo (n = 118)
Age, mean (SD), y	48.2 (18.4)	49.5 (19.9)
Sex, No. (%)		
Male	95 (79.2)	93 (78.8)
Female	25 (20.8)	25 (21.2)
Weight, mean (SD), kg	83.0 (20.9)	81.7 (16.0)
Height, mean (SD), cm	173.9 (9.2)	173.3 (8.6)
Body mass index, mean (SD)[b]	27.4 (6.3)	27.2 (4.8)
Clinical Frailty Scale, No. (%)[c]		
Very fit (category 1)	31 (25.8)	18 (15.3)
Well (category 2)	50 (41.7)	55 (46.6)
Managing well (category 3)	27 (22.5)	25 (21.2)
Vulnerable (category 4)	6 (5.0)	12 (10.2)
Mildly frail (category 5)	2 (1.7)	5 (4.2)
Moderately frail (category 6)	4 (3.3)	2 (1.7)
Severely frail (category 7)	0	1 (0.8)
Charlson Comorbidity Index score, mean (SD)[d]	0.3 (0.9)	0.5 (1.2)
Type of burn, No. (%)[e]		
Flame	84 (70.0)	81 (68.6)
Flash	20 (16.7)	26 (22.0)
Scald	14 (11.7)	6 (5.1)
Contact	1 (0.8)	2 (1.7)
Chemical	0	2 (1.7)
Other (specify)	1 (0.8)	0
Unknown	0	1 (0.8)
Burn size, mean (SD), % total body surface area	37.4 (15.0)	36.5 (14.3)
Inhalation injury present, No. (%)	35 (29.2)	34 (28.8)
SOFA score, mean (SD)[f]	3.2 (2.3)	3.4 (2.5)
APACHE II score, mean (SD)[g]	16.2 (7.8) [n = 95]	15.5 (7.0) [n = 101]
Mechanically ventilated at randomization, No. (%)	70 (58.3)	66 (55.9)
Traumatic brain injury, No. (%)	2 (1.7)	1 (0.8)
Trauma other than the burn injury, No. (%)	9 (7.5)	4 (3.4)
Time from ICU admission to first study dose, median (IQR), h	15.5 (6.4-21.1)	14.6 (7.3-20.5)
Time from injury to admission at study hospital, median (IQR), h	2.8 (1.2-5.8)	3.3 (1.7-5.6)

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment.

[a] Use of diuretics or electrolyte supplements before randomization was not recorded.

[b] Calculated as weight in kilograms divided by square of height in meters.

[c] Scale ranges from 1 (very fit) to 9 (terminally ill); higher scores indicate greater frailty.

[d] Index ranges from 0 to 37; higher scores indicate greater comorbidity burden. Additional comorbidities beyond those captured in the index were not systematically recorded.

[e] Type of burns are mutually exclusive.

[f] Score ranges from 0 to 24; higher scores indicate worse organ function.

[g] Score ranges from 0 to 71; higher scores indicate greater severity of illness.

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Table 2. Persistent Organ Dysfunction or Death at Day 28 (Primary Outcome)

Outcomes	No. (%)		Unadjusted			Adjusted RR (95% CI)		
	Vitamin C (n = 120)	Placebo (n = 118)	RD, % (exact 95% CI)	RR (95% CI)	Fisher exact test *P* value	No clustering by ICU	Clustering by ICU[a]	Model-based *P* value
Primary composite outcome								
Persistent organ dysfunction or death	49 (41)	35 (30)	11 (−1 to 23)	1.38 (0.97-1.96)	.08	1.28 (0.94-1.73)	1.28 (0.99-1.65)	.06
Components of the primary outcome								
Died	18 (15)	9 (8)	7 (−1 to 16)	1.97 (0.92-4.20)	.10	2.02 (1.04-3.92)	1.96 (1.32-2.90)	.001[b]
Inotropes or vasopressors	18 (15)	19 (16)	−1 (−10 to 8)	0.93 (0.52-1.68)	.86	0.82 (0.47-1.41)	0.82 (0.53-1.27)	.37
Kidney replacement therapy	4 (3)	5 (4)	−1 (−7 to 5)	0.79 (0.22-2.86)	.75	NA[c]	NA[c]	NA[c]
Mechanical ventilation	30 (25)	22 (19)	6 (−4 to 17)	1.34 (0.82-2.18)	.27	1.23 (0.78-1.93)	1.22 (0.85-1.75)	.27

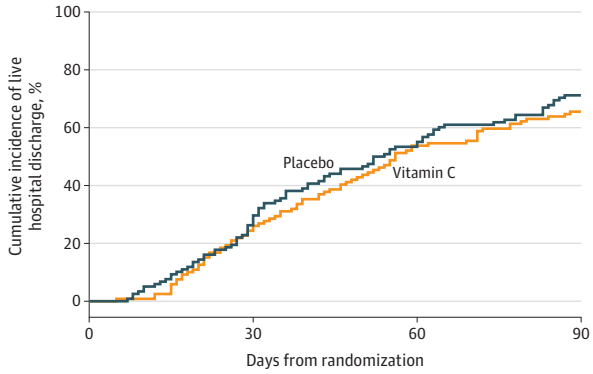
Abbreviations: ICU, intensive care unit; NA, not available; RD, risk difference; RR, relative risk.

[a] Estimated by modified Poisson regression with robust standard errors clustering by site and controlling for age, total body surface area, and mechanically ventilated at baseline.

[b] Adjusted model results for mortality including *P* value may be unreliable due to few events.

[c] Data too sparse for modeling.

Figure 2. Kaplan-Meier Cumulative Incidence of Live Discharge From Hospital Within 90 Days (Prespecified Main Secondary Outcome)



Vitamin C			
No. at risk 120	71	30	14
Deaths	18	26	28
Placebo			
No. at risk 118	71	35	16
Deaths	12	18	19

Patients were observed until death or index hospital discharge within 90 days of randomization. Curves show the proportion of randomized patients discharged alive over time. Death is a competing event precluding the possibility of hospital discharge. The adjusted subdistribution hazard ratio for time to discharge alive was 0.85 (95% CI, 0.62-1.16; *P* = .31). See **Table 3** for the medians and summary statistics for this outcome.

At 6 months, mortality was 25.9% (n = 30) in the vitamin C group and 20.2% (n = 23) in the placebo group (adjusted HR, 1.57 [95% CI, 0.89-2.75]; *P* = .12) (Table 3). Six-month Kaplan-Meier survival curves are shown in eFigure 4 in Supplement 3. Site-specific 6-month mortality rates ranged from 0% to 57.1% (eTable 6 in Supplement 3).

Gram-negative bacteremia occurred in 27 patients (22.5%) in the vitamin C group and 27 patients (22.9%) in the placebo group (Table 3). Other tertiary outcomes, including burn-related procedures and blood products administered, are reported in eTable 7 in Supplement 3.

Among surviving patients at 6 months, complete 36-Item Short Form Health Survey data were available for 139 of 185 eligible patients (77.5%), with no significant differences between groups in quality-of-life measures. No significant differences between groups were also found for 6-month activities of daily living (eTable 8 in Supplement 3).

Total median fluid volumes administered during ICU stay were 5908.6 mL (IQR, 3849.1-7557.5) in the vitamin C group vs 5096.4 mL (IQR, 3965.6-6903.5) in the placebo group (eTable 9 in Supplement 3). Fluid balance was also similar between groups (median, 2728.9 mL vs 2557.0 mL). Daily fluid volumes over the first 8 days are shown in eFigure 5 in Supplement 3.

Safety and Adverse Event Outcomes

Acute kidney injury occurred in 18 patients (15.0%) in the vitamin C group and 13 patients (11.0%) in the placebo group (*P* = .57) (eTable 10 in Supplement 3). KRT was initiated in 13 patients (10.8%) in the vitamin C group and 7 patients (5.9%) in the placebo group (*P* = .24), with duration of KRT among users of 21.3 (19.8) days vs 26.0 (25.9) days (*P* = .72). Hypoglycemia occurred in 6 patients in the vitamin C group vs 3 patients in the placebo group (*P* = .50). Other events of interest including new diagnosis of oxalate kidney stones, severe hemolysis, severe acid-base/electrolyte imbalances, and refractory hypoglycemia were not reported in either group.

Twelve serious adverse events were reported: 9 in the vitamin C group and 3 in the placebo group (eTable 11 in Supplement 3).

Discussion

In this international, multicenter, randomized clinical trial involving patients with severe burn injury, high-dose intrave-

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Table 3. Main Secondary and Tertiary Outcomes

Outcome	Vitamin C (n = 120)	Placebo (n = 118)	Measure (95% CI)		*P* value[a]
			Unadjusted absolute difference	HR or RR (95% CI)	
Main secondary outcome					
Days to hospital discharge alive within 90 d, median (IQR)	56.0 (30.0-Undefined)[b]	53.0 (29.0-Undefined)[b]	3.0 (−11.0 to 25.0)	Subdistribution HR Unadjusted: 0.87 (0.64-1.19) Adjusted: 0.85 (0.62-1.16)[c]	.31
Cumulative incidence of hospital discharge alive within 90 d, % (95% CI)	65.5 (56.2-73.4)	71.2 (62.0-78.5)	−5.6 (−17.6 to 6.3)		
Tertiary outcomes					
ICU readmission, No. (%)	3 (2.5)	4 (3.4)	−1 (−6 to 4)	NA[d]	
Mortality, No. (%)					
ICU	27 (22.5)	18 (15.3)	7 (−3 to 17)	Adjusted RR: 1.43 (1.00-2.04)[c]	.05
Hospital	28 (23.3)	19 (16.1)	7 (−3 to 18)	Adjusted RR: 1.44 (1.03-2.00)[c]	.03
Sixth-month[e]	30 (25.9)	23 (20.2)	6 (−5 to 17)	Adjusted HR: 1.57 (0.89-2.75)[c]	.12
Duration outcomes, median (IQR)					
Days to discharge alive from ICU	52.0 (24.0-Undefined)[b]	42.5 (25.0-Undefined)[b]	9 (−9 to 23)	Adjusted HR: 0.87 (0.64-1.18)[c,f]	
Days to discharge alive from hospital among hospital survivors	44.0 (25.0-71.0)	43.0 (27.0-78.0)	1 (−14 to 15)	Adjusted HR: 1.01 (0.74-1.38)[c]	
Days of mechanical ventilation	6.5 (0.0-29.5)	5.0 (0.0-22.0)	NA[d]	NA[d]	
Days of dialysis	0.0 (0.0-0.0)	0.0 (0.0-0.0)	NA[d]	NA[d]	
Days of vasopressor use	3.0 (0.0-15.0)	2.0 (0.0-13.0)	NA[d]	NA[d]	
Gram-negative bacteremia, No. (%)	27 (22.5)	27 (22.9)	0 (−11 to 11)	Adjusted RR: 0.94 (0.67-1.32)[c]	

Abbreviations: HR, hazard ratio; ICU, intensive care unit; NA, not available; RR, relative risk.

[a] *P* values are based on the adjusted model and are only reported for mortality to be consistent with the prespecified analysis plan, which specified that *P* values would only be reported for the primary, secondary, and safety outcomes including mortality.

[b] Undefined indicates the quantile was never reached.

[c] Adjusted for age, total body surface area, and mechanically ventilated at baseline in addition to site.

[d] Data too sparse for modeling or many patients have 0 days, and no summary measure is particularly helpful.

[e] Percentages are based on Kaplan-Meier estimates rather than raw percentages.

[f] The adjusted HR for days to discharge alive from ICU is a subdistribution hazard ratio with death as a competing risk.

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nous vitamin C administered during the first 96 hours of resuscitation did not reduce the primary outcome of 28-day mortality and persistent organ dysfunction or of any of the other secondary outcomes. The observed rate of death and persistent organ dysfunction was higher in the vitamin C group, crossing the prespecified futility/harm threshold at the first interim analysis and prompting early trial termination. Twenty-eight-day, ICU, and hospital mortality were higher in patients who received vitamin C.

These findings challenge the long-held hypothesis that high-dose vitamin C, through its antioxidant and endothelial protective properties, would confer clinically meaningful benefits in this population.[10,11,18,19] The regimen tested was intended as pharmaconutrition—using supraphysiological doses to modulate biological pathways—far exceeding standard repletion doses. Early clinical studies, including a landmark trial by Tanaka et al,[11] demonstrated reduced fluid resuscitation requirements and shorter ventilation duration with high-dose intravenous vitamin C. Subsequent small trials and retrospective analyses consistently reported fluid-sparing effects but were underpowered for patient-centered outcomes.[14,18,20-22] Based on this limited evidence, some international nutrition guidelines have suggested vitamin C supplementation for treatment of major burns.[13]

In contrast, the present trial found no reduced organ dysfunction or improvement in time to discharge alive from the hospital within 90 days and with a significant increase in 28-day, ICU, and hospital mortality rates in the vitamin C group. These results align with those from the recent LOVIT trial in patients with septic shock, which used an identical dosing regimen and found increased risk of death and persistent organ dysfunction with intravenous vitamin C monotherapy.[16] While patients with burn injuries differ fundamentally from patients with sepsis in their pathophysiology, fluid dynamics, and mortality risk profile, the convergence of harm signals across these distinct populations raises concern.[15,18] Several biologically plausible mechanisms may explain the overall lack of positive treatment effects and signal of harm. First, ascorbic acid is metabolized to oxalate, which can crystallize in kidney tubules and cause oxalate nephropathy, particularly in the setting of hypovolemia and acidic urine common during burn resuscitation.[5,23-25] Although no cases of oxalate kidney stones were reported because they are not always clinically apparent, KRT was initiated almost 2 times more frequently in the vitamin C group. Second, the complex redox biology of critical illness must be considered; in the profoundly dysregulated metabolic state following major burns, high-dose vitamin C may paradoxically act as a pro-oxidant or disrupt essential redox signaling.[26] Third, the specific formulation used requires dilution from a hyperosmolar stock to isotonicity prior to administration. While preparation followed standardized protocols, the metabolic consequences of administering a large acid load in critically ill patients with impaired buffering capacity remain uncertain.[27]

The discordance between these findings and those from earlier trials warrants careful examination. Earlier studies were predominantly small, single-center, and often unblinded, conducted in an era of more liberal fluid resuscitation strategies.[11,14,21,28] The moderate fluid-sparing effects observed in these earlier trials may represent the maximum achievable benefit, which in the context of updated protocolized resuscitation strategies appears insufficient to translate into clinically detectable improved organ function or survival.

Limitations

This trial has several limitations. First, early termination for futility or harm after the interim analysis limits the precision of effect estimates and may overestimate the harm of the intervention. However, simulations suggest that this negative bias is likely small. The prespecified futility/harm threshold suggested that proceeding would be futile, and there was a signal toward increased mortality and persistent organ dysfunction in the vitamin C group, prompting the DSMB to recommend termination of the trial, a decision that underscores the clinical relevance of the observed safety. Second, the final sample size was smaller than originally intended, thus reducing statistical power for all outcomes. Third, the trial was not powered to detect differences in rare safety events such as oxalate nephropathy, and no cases were reported; however, a possible subclinical kidney injury cannot be excluded. Fourth, several sites enrolled only a small number of patients (≤5), which may have resulted in incomplete randomization blocks at those sites, allowing within-site treatment-group imbalances and sparse or absent outcome events, thereby slightly reducing precision.

Conclusions

Among patients with severe burn injury, high-dose intravenous vitamin C administered during the first 96 hours of resuscitation did not reduce the primary composite outcome of 28-day mortality and persistent organ dysfunction and is possibly harmful.

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Author Affiliations: Department of Anaesthesiology, Intensive Care, Emergency and Pain Medicine, University Hospital Würzburg, Würzburg, Germany (Stoppe, Meybohm, Dresen, Güttler, Lee); Department of Cardiac Anesthesiology and Intensive Care Medicine, Deutsches Herzzentrum der Charité, Berlin, Germany (Stoppe, Lee); German Centre for Cardiovascular Research (DZHK), Berlin, Germany (Stoppe); Center for Outcomes Research, UTHealth, Houston, Texas (Stoppe); Department of Intensive Care Medicine, University Hospital RWTH, Aachen, Germany (Hill); US Army Institute of Surgical Research Burn Center, JBSA Fort Sam Houston, Texas (Cancio, Pruskowski); Kingston Health Sciences Centre—Research Institute, Kingston, Ontario, Canada (Day); Population Health and Optimal Health Practices Research Unit (Trauma-Emergency-Critical Care Medicine), CHU de Québec—Université Laval Research Center, Québec City, Québec, Canada (Turgeon); Division of Critical Care Medicine, Department of Anesthesiology and Critical Care Medicine, Université Laval, Québec City, Québec, Canada (Turgeon); Harborview Medical Center, Seattle, Washington (Pham); CHUM, Service of Intensive Care, Department of Medicine, Université de Montréal, Montréal, Québec, Canada (Bélisle); Hospital Central Dr Ignacio Morones Prieto, San Luis Potosi, Mexico (Martínez-Jiménez); Department of Anesthesiology and Critical Care Medicine,

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Merheim Medical Center, Hospitals of Cologne, Witten/Herdecke University, Cologne, Germany (Limper); Klinikum St Georg, Leipzig, Germany (Gille); The Ohio State University Medical Center, Columbus (Wisler); Bridgeport Hospital & Burn Center, Yale New Haven Health, Bridgeport, Connecticut (Savetamal); Mercy Research Institute, St Louis, Missouri (Pollack); Centro Nacional de Quemaduras y Cirugía Reconstructiva, Asuncion, Paraguay (Grau Domínguez); Pôle centre des brûlés, chirurgie plastique, dermatologie et banque de peau, Centre de Traitement de Brûlés, Grand Hôpital de Charleroi, Gilly, Belgium (Jennes); MedStar Washington Hospital Center, Georgetown University, Washington, DC (Shupp); Burn Program and Centre for Burn Research, Hamilton Health Sciences, Department of Surgery, McMaster University, Hamilton, Ontario, Canada (Jeschke); Department of Intensive Care Medicine, Ghent University Hospital, and Data Science Institute, Ghent University Hospital, Ghent, Belgium (Colpaert); Department of Internal Medicine and Pediatrics, Faculty of Medicine and Health Sciences, Ghent University, Ghent, Belgium (Colpaert); Department of Hand, Plastic and Reconstructive Surgery, Burn Trauma Center, BG Trauma Center Ludwigshafen, University of Heidelberg, Germany (Hundeshagen); Department of Plastic, Hand and Burn Surgery, University Hospital RWTH Aachen, Aachen, Germany (Beier); Siriraj Hospital, Bangkok, Thailand (Muangman); Mahidol University, Bangkok, Thailand (Muangman); Hospital San Juan de Dios, San José, Costa Rica (Echeverri McCandless); German Institute of Human Nutrition, Potsdam-Rehbruecke, Nuthetal, Germany (Grune, Weber); Department of Dietetics and Nutrition, Ng Teng Fong General Hospital, Singapore (Lew); Faculty of Health and Social Sciences, Singapore Institute of Technology, Singapore (Lew); Department of Critical Care Medicine, Queen's University at Kingston, Kingston, Ontario, Canada (Jiang, Froese, Dansereau, Heyland); Department of Anaesthesiology, Faculty of Medicine, Universiti Malaya, Kuala Lumpur, Malaysia (Lee).

Author Contributions: Drs Stoppe and Heyland had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Stoppe, Hill, Cancio, Day, Pruskowski, Turgeon, Martínez-Jiménez, Jeschke, Colpaert, Hundeshagen, Muangman, Heyland.
Acquisition, analysis, or interpretation of data: Stoppe, Hill, Day, Turgeon, Pham, Bélisle, Martínez-Jiménez, Limper, Gille, Wisler, Savetamal, Pollack, Grau Dominguez, Jennes, Shupp, Jeschke, Hundeshagen, Beier, Echeverri McCandless, Meybohm, Grune, Dresen, Weber, Güttler, Lew, Jiang, Froese, Dansereau, Lee, Heyland.
Drafting of the manuscript: Stoppe, Day, Turgeon, Martínez-Jiménez, Wisler, Savetamal, Shupp, Colpaert, Dresen, Jiang.
Critical review of the manuscript for important intellectual content: Hill, Cancio, Day, Pruskowski, Turgeon, Pham, Bélisle, Martínez-Jiménez, Limper, Gille, Wisler, Savetamal, Pollack, Grau Dominguez, Jennes, Shupp, Jeschke, Colpaert, Hundeshagen, Beier, Muangman, Echeverri McCandless, Meybohm, Grune, Dresen, Weber, Güttler, Lew, Froese, Dansereau, Lee, Heyland.
Statistical analysis: Stoppe, Lew, Day, Jiang.
Obtained funding: Stoppe, Hill, Wisler, Beier, Heyland.
Administrative, technical, or material support: Stoppe, Hill, Cancio, Pruskowski, Pham, Limper, Pollack, Shupp, Jeschke, Hundeshagen, Beier, Muangman, Echeverri McCandless, Dresen, Güttler, Froese, Dansereau, Lee, Heyland.
Supervision: Stoppe, Hill, Cancio, Bélisle, Wisler, Pollack, Grau Dominguez, Shupp, Jeschke, Hundeshagen, Muangman, Meybohm, Grune, Dansereau, Heyland.

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